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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	27

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/766,350	CHATTERJEE ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,26-65 and 67-97* is/are pending in the application.

4a) Of the above claim(s) *6-19,38,41,44-53,57 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 20-24, 26-37, 39, 40, 42, 43, 54-56, 59-65,and 67-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-24,26-65 and 67-97* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. The amendment filed November 7, 2001 (Paper No. 31) is acknowledged and has been entered. Claims 26 and 33 have been amended. Claims 74-97 have been added.

2. Claims 1-24, 26-65, and 67-97 are pending in the application. Claims 6-19, 38, 41, 44-53, 57, and 58 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made with traverse in Paper No. 9.

3. Claims 1-5, 20-24, 26-37, 39, 40, 42, 43, 54-56, 59-65, and 67-97 are currently under prosecution.

Election/Restrictions

4. Applicants' request for rejoinder of presently excluded method claims in Paper No. 31 is acknowledged. Applicants' request is denied. The application presently recites claims drawn to more than one method for using the product, and these inventions were restricted into separate groups in the Office action mailed October 3, 1997. Furthermore, the product claims are not presently allowable.

Claim Rejections Withdrawn

5. Unless specifically reiterated below, the grounds of objection and rejection set forth in the previous Office actions have been withdrawn.

Specification

6. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks

should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

For example, the trademarks ALUGEL and SIGMASTAT are improperly used on pages 120 and 141, respectively; however, this is *not* an exhaustive list of the improperly used trademarks that appear in the application.

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

7. Claim 36 recites "polymeric 11D10 polypeptide". The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Appropriate correction is required; or alternatively, Applicants might obviate this issue by pointing to specific disclosure(s) in the specification that are believed to provide proper antecedent basis for the claim language.

Claim Objections

8. Claims 5, 23, 24, 69, 70, 75, 78, 80, 86, 90, 94, and 97 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants are required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form.

Recitations of inherent properties or intended use cannot be relied upon to further limit the subject matter of the claim or claims from which a claim depends.

9. Claims 4, 40, 42, 60, 73, 74, 75, 76, and 84 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim(s) 1, 37, 39, 59, 35, 37 and 40, 37 and 40, 43,

and 35 and 73, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

10. Claims 77 and 96 are objected to because a polypeptide of claim 20 cannot comprise the three complementarity-determining regions (CDRs) of the light chain variable region of the monoclonal antibody 11D10 **and** the three CDRs of the heavy chain variable region of the monoclonal antibody 11D10, as required by claim 77, because claim 20 requires the polypeptide to comprise one or the other, *not both.*

Claim Rejections – 35 USC § 101

11. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

12. Claims 1, 92, and 97 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1, 92, and 97 encompass a naturally occurring product. For example, the hybridoma deposited under ATCC Accession No. HB-12020 naturally produces a monoclonal anti-idiotype antibody that fulfills the limitations of the claims. Furthermore, the hybridoma was derived from a naturally occurring lymphocyte that also naturally produces the monoclonal antibody 11D10, which also fulfills the limitations of the claims. As the claims are written, the subject matter of the claims cannot be distinguished from such naturally occurring products.

13. Claims 20-24, 26-30, 34, 36, 39, 42, 56, 61-63, 67, and 68 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility, or a well-established utility.

Claims 20-24, 26-30, 34, 36, 42, 56, 61, 67, and 68 are drawn to a polypeptide, or to a fusion polypeptide comprising said polypeptide, wherein said polypeptide comprises an immunoglobulin variable region containing the three complementarity-determining regions (CDRs) of the light chain, **or** the heavy chain of monoclonal antibody 11D10, and wherein said polypeptide has the ability to stimulate a specific immune response against human milk fat globule (HMFG).

Claims 39, 62, and 63 are drawn to a composition comprising a polypeptide, wherein said polypeptide comprises an immunoglobulin variable region containing the three complementarity-determining regions (CDRs) of the light chain, **or** the heavy chain of monoclonal antibody 11D10, and wherein said polypeptide has the ability to stimulate a specific immune response against human milk fat globule (HMFG).

The specification asserts that the invention can be used to elicit an anti-HMFG immune response in a mammal to induce antitumor immunity in the mammal, but this asserted utility lacks credibility. Notably the specification does not disclose working exemplification of the use of the claimed invention to elicit an anti-HMFG immunological response in a mammal. In fact, the specification only demonstrates the use of an antibody to elicit an anti-HMFG immunological response in a mammal. While it is credible that a polynucleotide encoding a single-chain antibody derived from the amino acid sequences of which monoclonal antibody 11D10 is composed, upon expression in a mammal, would be capable of eliciting the same anti-HMFG immunological response that is elicited by the monoclonal antibody 11D10, it is not credible that any polypeptide comprising only the variable region of the light chain, or the heavy chain of monoclonal antibody 11D10 would be capable of doing so. There is no factual evidence in the specification that would support the asserted utility of the claimed invention; and for the reasons stated in the grounds of rejection of the claims under 35 USC § 112, first paragraph, one skilled in the art would not accept the assertion that the claimed invention can be used to elicit an anti-HMFG immunological response in a mammal. In particular, Benvenuti, et al (*Gene Therapy* **7**: 605-611, 2000) teach that anti-idiotypic DNA vaccines, such as the vaccines disclosed in the specification, which comprises the polynucleotide sequences encoding a polypeptide comprising one or both of the

immunoglobulin variable regions of monoclonal antibody 11D10, require the presence of both variable region genes for tumor protection. Consequently, one would not expect a mere fragment of a variable region of the monoclonal antibody to be capable of eliciting the same immunological response that the monoclonal antibody elicits in a mammal. Therefore, the asserted utility of the invention, which appears specific and substantial, is not credible.

The utility of the claimed invention is not well established. If the asserted utility is indicated to be nonspecific and insubstantial, because the claimed invention is not supported by a specific and substantial asserted utility, the credibility of the utility cannot be assessed.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 20-24, 26-30, 34, 36, 39, 42, 56, 61-63, 67, and 68 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility, a credible asserted utility, or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention, because one skilled in the art could not make and/or use the claimed invention with a reasonable expectation of success without need to perform undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or

unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

As stated in the 35 USC § 101 rejection above, the specification fails to disclose sufficient guidance and direction to enable one skilled in the art to make and use the claimed invention. Moreover, there is no working exemplification of the use of the claimed invention to stimulate a specific immune response against HMFG or to induce antitumor immunity in a mammal. In the absence of working exemplification commensurate in scope with the claims, one skilled in the art cannot predict whether the claimed invention can be used successfully to elicit an anti-HMFG immunological response in a mammal or to induce antitumor immunity in a mammal, because the art is highly unpredictable. Nonetheless, based upon the state of the art, as evidenced by the teachings of Benvenuti, et al, one would not expect the claimed invention to be capable of eliciting an anti-HMFG immunological response. Although Benvenuti, et al teach that a polynucleotide encoding only the variable heavy chain of an anti-idiotypic antibody can elicit an immunological response in a mammal, Benvenuti, et al found that the polynucleotide is not capable of inducing protective antitumor immunity in a mammal. Based on the teachings of Benvenuti, et al, one skilled in the art would not be able to predict whether a polynucleotide encoding only the variable light chain of an anti-idiotypic antibody would be capable of eliciting an immunological response in a mammal, but it seems unlikely that the polynucleotide would be capable of inducing protective antitumor immunity in a mammal, since the polynucleotide encoding the heavy chain variable region of the antibody could not do so.

16. Claims 1-5, 20-24, 26-37, 39, 40, 42, 43, 54-56, 59-65, and 67-97 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using the mouse monoclonal antibody 11D10, the hybridoma that produces mouse monoclonal antibody 11D10, a chimeric or humanized version of mouse monoclonal antibody 11D10, the disclosed single chain Fv antibody derived from mouse monoclonal antibody 11D10, an antigen-binding fragment of mouse monoclonal antibody 11D10, and a fusion polypeptide comprising monoclonal antibody 11D10, said

antigen-binding fragment thereof, said single chain Fv antibody, or said chimeric or humanized version thereof, does not reasonably provide enablement for making and/or using a monoclonal antibody produced by the progeny of the hybridoma that produces monoclonal antibody 11D10, or said progeny, or a polypeptide that comprises a region of either the heavy chain or the light chain of monoclonal antibody 11D10, or a polypeptide that comprises the three complementarity-determining regions (CDRs) of either or both of the light and heavy chains of monoclonal antibody 11D10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification disclosed therein would be insufficient to enable the skilled artisan to have a reasonable expectation of successfully making and using the claimed invention without having the need to first perform additional, and an undue amount of experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. An analysis of the content of the specification and simultaneously weighing each of these factors indicates that one skilled in the art would not be able to make and/or use the claimed invention with a reasonable expectation of success without need to first perform undue experimentation. Therefore, the disclosure is insufficient to meet the requirements set forth under 35 USC §112, first paragraph.

The state of the art and the relative skill of those in the art is such that the production of chimeric antibodies, which comprise the light and heavy chain variable domains of a murine monoclonal antibody and the light and heavy chain constant domains of a human antibody is routine and conventional, since the methodology

required is well-established and because chimeric antibodies are generally less immunogenic than mouse antibodies, chimeric antibodies are more suitable for use in humans. Furthermore, it is rapidly becoming routine in the art to produce recombinant single chain antibodies comprising the variable domain of a monoclonal antibody's light chain joined by a polypeptide linker to the variable domain of a monoclonal antibody's heavy chain, where both the light and heavy chain variable domains contain the three complementarity-determining regions (CDRs) of those chains in approximately the same sequential and spatial arrangement as that in which they occur in the natural antibody. Moreover, it will become routine in the art to produce reshaped antibodies, e.g., humanized or Primatized™ antibodies, which are recombinant antibodies composed of light and heavy chain variable domains comprising the complementarity-determining regions (CDRs) of a murine monoclonal antibody but the framework or scaffolding regions of a human antibody; as the reshaped antibodies are generally even less immunogenic than chimeric antibodies, it will has become conventional to use reshaped antibodies as therapeutic agents in humans.

However, it is not routine or conventional in the art to make and use a polypeptide consisting of only a variable domain of either the light or the heavy chain of an antibody, because neither the light nor the heavy chain is inherently immunogenic of *a specific anti-paratope immune response*.

Despite recent advances in technology, antibody engineering is subject to a high degree of unpredictability, so that empirical determination is essential. Antibody structure is highly complex and very sensitive to even small alterations in amino acid sequence. The combination of the two variable regions of a light chain and a heavy chain defines the particular antigen-binding region or paratope of an antibody. An antibody binds an antigen by virtue of its ability to form a sterically and energetically favored molecular complex by a process that is dependent upon the complementary alignment of a matrix of molecular determinants contained in the so-called "complementarity-determining regions" (CDRs) of the variable chains of the antibody with a matrix antigenic determinants contained by the antigen's epitope. Since the constant regions are not unique to an antibody, it is the conformation of the paratope of

an antibody that defines its antigenicity, i.e., its idiotype. Immunizing a mammal with an antibody that specifically binds the epitope of the antigen produces an anti-idiotypic antibody. The paratope of an anti-idiotypic antibody mimics the complexities of the three-dimensional structure of an epitope present on an antigen to which the idiotypic antibody binds, because the anti-idiotypic antibody comprises a matrix of molecular determinants that are "recognized" or are complemented by the matrix of antigenic determinants contained by the idiotypic antibody's idiotype, which necessarily complement the antigenic determinants of the antigen's epitope. In the instant case, the specification teaches that an animal was immunized with monoclonal antibody BrE-1, which specifically binds an epitope of a human milk fat globule (HMFG) protein, to produce the anti-idiotypic antibody, namely monoclonal antibody 11D10. The specification, then, teaches that immunizing an animal with monoclonal antibody 11D10 elicits the production of anti-anti-idiotypic antibodies in the animal that specifically bind the anti-idiotypic antibody's paratope, which mimics the epitope to which BrE-1 binds, and therefore immunizing the animal with monoclonal antibody 11D10 elicits the production of antibodies in the animal that specifically bind the epitope of HMFG to which the monoclonal antibody BrE-1 binds.

In view of the complexity of the antibody, the state of the art, and the amount of working exemplification disclosed in the specification, it seems that the skilled artisan would not have a reasonable expectation of successfully producing and using the claimed invention, which includes a multitude of potentially non-working embodiments. For example, the skilled artisan would not have a reasonable expectation of successfully making and using a polypeptide that comprises only the variable region of light or the heavy chain of a monoclonal antibody, or a mere portion thereof. Based upon the structure of an antibody and the nature of its immunogenicity, as discussed in the paragraph above, it is highly unpredictable that the polypeptide encoded by such a polynucleotide would be capable of stimulating a specific anti-HMFG immunological response.

In fact, it appears that immunizing a mammal with a DNA molecule comprising a polynucleotide sequence encoding only one of the variable regions of an antibody

cannot effectively elicit the desired immune response. Benvenuti, et al (*Gene Therapy* **7**: 605-611, 2000) and Benvenuti, et al (*Gene Therapy* **8**: 1555-1561, 2001) teach that a single-chain anti-idiotypic antibody comprising the variable regions of both the light and heavy chains of a parental antibody effectively elicits an immunological response in mammals, producing antibodies that are specifically reactive with the antigen to which the idiotype binds. Since it is difficult to demonstrate the absence of an immunological response in a mammal, Benvenuti, et al determined the reactivity of the immune sera produced in mammals immunized with the DNA encoding a single-chain antibody with a polypeptide comprising only one or the other variable region of either the light or heavy chain of the parental antibody. Benvenuti, et al (2001) found no immune reactivity with polypeptides comprising only one or the other variable region of either the light or heavy chain of the parental antibody, which suggests that only antibodies that recognize determinants resulting from the combination of the variable regions of the light and heavy chains, but not present in the isolated variable regions are produced in response to anti-idiotypic immunization. Benvenuti, et al (2001) conclude, "[t]hese findings indicate that presentation of properly folded idiotypes results in a highly specific antibody response directed exclusively to private idiotypic determinants of the V_L/V_H combination of the immunogen" (abstract). Because the specific and desired immunogenicity of the anti-idiotypic antibody predominantly depends upon its precise quaternary structure, it seems evident that the conformation of a polypeptide comprising only a single variable domain of either the light or heavy chain of an antibody may not sufficiently resemble the conformation of the complex of the combined variable domains of both the light and heavy chains and might not faithfully reproduce the idiotype of the antibody to elicit a specific immune response, which would result in the production of antibodies or T-cells with the necessary specificity, avidity, and affinity to protect a mammal against a tumor bearing HMFG, which is an asserted utility of the claimed invention. In the absence of working exemplification, the skilled artisan would therefore not accept the assertion the claimed polypeptides, especially those encompassed by claims 20 and 39, would be capable of stimulating a specific immune response against HMFG.

Despite the fact that the claims recite limitations requiring the polypeptides to have the ability to stimulate a specific immune response against HMFG, the specification only teaches methods for making one or two embodiments, and because the claims encompass a large genus of polypeptides with highly variant structures, the amount of guidance, direction, and exemplification are not reasonably commensurate in scope with the claims.

Although Benvenuti, et al found that immunizing the animal with DNA encoding a polypeptide comprising only one or the other variable regions of the either the light or the heavy chain of the antibody resulted in the production of some antibodies, in the present case, the specification fails to teach that the variable regions of light and heavy chains of monoclonal antibody 11D10 are capable of eliciting any specific anti-HMFG immune response. Based upon the teachings of Benvenuti, et al, in the absence of working exemplification that is reasonably commensurate in scope with the claims, the skilled artisan would not accept the assertion that the immune response elicited by immunizing a mammal with only one or the other of the variable regions of either the light or heavy chains of monoclonal antibody 11D10, would be sufficient to make the invention therapeutically useful. Furthermore, as discussed in the Office Action mailed March 31, 1999 (Paper No. 19), because of the sensitivity of the antibody's structure and function to amino acid substitutions, as evidenced by the teachings of Rudikoff, et al, Panka, et al, Adair, et al, and Amit, et al, again in the in the absence of working exemplification that is reasonably commensurate in scope with the claims, the skilled artisan would not accept the assertion an antibody or a polypeptide comprising one or both variable regions of the light or heavy chains of monoclonal antibody 11D10, in which the exact spatial and sequential arrangement of the CDRs of monoclonal antibody 11D10 is not faithfully reiterated, would be retain the specificity, affinity, or avidity of the monoclonal antibody, or that the immune response elicited by immunizing a mammal with a polynucleotide encoding such antibody or a polypeptide would be sufficient to make the invention useful.

Although the conformation, i.e., three-dimensional structure of an antibody's antigen-binding region is highly sensitive to amino acid variation, as evidenced by the

teachings of Rudikoff, et al, Panka, et al, Adair, et al, and Amit, et al, provided that the recombinant antibody comprises both variable regions, it has become increasingly more routine to produce recombinant antibodies that retain the antigen-binding specificity and affinity of the natural antibody from the amino acid sequence of which the recombinants are derived. Nevertheless, as stated in the 35 USC § 101 rejection above, the skilled artisan could not predictably make or predictably use with a reasonable expectation of success, a polypeptide comprising only a portion of a variable domain of the either the light or heavy chains of monoclonal antibody 11D10 to produce an anti-HMFG immunological response in a mammal. Moreover, an antibody comprising the CDRs of both the light and heavy chains of monoclonal antibody 11D10 would not be expected to adopt a three-dimensional structure that would mimic the paratope of the monoclonal antibody and be capable of eliciting an anti-HMFG immunological response in a mammal if the sequential and spatial organization of the CDRs is not conserved in the structure of the antibody.

Consider, for example, the antibody described by Kofler, et al (*Journal of Clinical Investigation* **82**: 852-860, 1988). Despite the fact that the antibody of Kofler, et al binds a DNA molecule, the antibody is encompassed by the present claims, since the antibody comprises a region of both the light and heavy chains of monoclonal antibody 11D10. The specification does not provide any guidance, direction, or exemplification that would be reasonably considered to enable one to make and use the antibody of Kofler, et al.

Additionally, it is well established in the art that a linker is an essential component of a single-chain antibody. While the length and composition of the linker can significantly alter the yield and the biological activity of a single-chain antibody, there is sufficient guidance and direction in the art and the specification to enable the skilled artisan to determine the optimal length and composition of the linker of a single-chain antibody comprising the variable domains of the light and heavy chains of monoclonal antibody 11D10. However, one skilled in the art would not expect to be able to produce and use with a reasonable expectation of success, a single-chain antibody that does not comprise a suitable linker; and certainly in the absence of working exemplification and

adequate guidance, undue experimentation would be required to do so. Desplancq, et al (*Protein Engineering* **7**: 1027-1033, 1994) have characterized the properties of several different single-chain antibodies having linkers of different lengths, which are composed of up to six repeats of the amino acid sequence glyc-gly-gly-gly-ser. Desplancq, et al disclose that a single-chain antibody having the organization VH-linker-VL, i.e., an antibody in which the variable light chain is positioned at the amino-terminus separated by the linker from the variable heavy chain at the carboxyl-terminus, has "good binding affinity" only when the linker is composed of six repeats of the amino acid sequence. Desplancq, et al teach that shorter linkers interfere with the proper folding of the light and heavy chains, so that the amino acids of light and heavy chains are not able to make the necessary contributions to the antigen-binding site. Desplancq, et al found that an antibody having a linker composed of the amino acid sequence set forth in SEQ ID NO: 35 had relatively poor binding activity. Thus, one skilled in the art would not reasonably expect to successfully use a fusion polypeptide according to claims 32 and 79 without the need to first perform additional, undue experimentation.

Furthermore, as the progeny of the hybridoma producing monoclonal antibody 11D10 may or may not be completely identical to the original cell due to mutation or other adaptation, but must produce a monoclonal antibody that maintains the ability to escape immune tolerance, i.e., to cause an immune response against HMFG, the specification would necessarily have to provide guidance and direction, if not exemplification to enable the skilled artisan to make and use the claimed invention. For example, the claims encompass progeny of the parental hybridoma cell line that produce an antibody that differs structurally from monoclonal antibody 11D10; but for the reasons set forth above, the art is highly unpredictable, and since the specification does not teach which amino acids might be deleted, inserted, or substituted, where or by what other amino acids, the amount of guidance set forth in the disclosure would be insufficient to enable the skilled artisan to have a reasonable expectation of success absent a need to perform additional, undue experimentation.

Finally, Applicants have provided convincing evidence that that one skilled in the art could not reasonably expect to be able to reproduce the hybridoma that produces

the antibody 11D10. For example, see paragraph 2 of page 11 of Paper No. 14. Accordingly, Applicants have traversed the grounds of rejection under 35 USC §§ 102 and/or 103 arguing that if one did not have access to the hybridoma that produces the antibody, one could not expect to produce the antibody, unless one had knowledge of the amino acid sequence of the antibody. Applicants have further argued that the amino acid sequence of the antibody was not disclosed before the filing date of the application and that without access to the antibody or the hybridoma producing the antibody, one skilled in the art could not determine the amino acid sequence of the antibody. It stands to reason, therefore, that to meet the requirements set forth under 35 USC § 112, first paragraph, the disclosure must teach the amino acid sequence of the antibody. However, there is evidence suggesting that the amino acid sequence set forth in this application is not the amino acid sequence of the antibody. Tripathi, et al (*Hybridoma* **18**: 193-202, 1999) teach the amino acid sequence of the light chain of monoclonal antibody 11D10. Tripathi, et al disclose Applicants' own work; yet the amino acid sequence of the antibody disclosed by Tripathi, et al differs from Applicants' disclosed amino acid sequence of the light chain of the antibody. Upon the presumption that the amino acid sequence taught by Tripathi, et al is, in fact, the actual amino acid sequence of the antibody, it cannot be determined if an antibody having Applicants' disclosed amino acid sequence can or cannot be used in accordance with the assertions set forth in this application due to the lack of predictability in the art, as discussed above. Regardless of the usefulness of an antibody having Applicants' disclosed amino acid sequence, given the benefit of Applicants' disclosure, one skilled in the art could not reasonably expect to make monoclonal antibody 11D10 without having the hybridoma that produces the antibody.

In summary, the amount of exemplification, guidance, and direction in the specification is not reasonably commensurate in scope with the claims and would not be sufficient to enable the skilled artisan to make and use the claimed invention with a reasonable expectation of success without need to perform undue experimentation. Accordingly, the disclosure fails to meet the requirements set forth under 35 USC § 112, first paragraph.

17. Claims 1-5, 20-24, 26-37, 39, 40, 42, 43, 54-56, 59-65, and 67-97 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 4 is drawn to a genus of antibodies having all the identifying characteristics of monoclonal antibody 11D10, or of another antibody produced by the progeny of the hybridoma cell line deposited under ATCC accession no. HB 12020. Claim 5 is drawn to a genus of hybridomas having all the identifying characteristics of the hybridoma that produces monoclonal antibody 11D10, or of another hybridoma, which is the progeny of the hybridoma cell line deposited under ATCC accession no. HB 12020. The specification discloses that identifying characteristics can be structural and/or functional features (page 19). However, the specification does not describe all the identifying structural and functional characteristics of monoclonal antibody 11D10; moreover, the specification has not does not describe any of the identifying structural and functional features of an antibody produced by the progeny of the hybridoma that produces monoclonal antibody 11D10. Furthermore, the specification does not describe all the identifying structural and functional features of the hybridoma, or its progeny. The skilled artisan could not immediately recognize the identifying characteristics of the antibodies or the hybridomas producing the antibodies to which the claims are drawn, and therefore the skilled artisan could not immediately recognize, or distinguish at least a substantial number of members of the claimed genera of antibodies and hybridomas.

Claim 20, and its dependent claims, and claims 39, 62, and 63 are drawn to a genus of polypeptides comprising a region of monoclonal antibody 11D10 containing the three light chain complementarity-determining regions (CDRs) or alternatively a region of monoclonal antibody 11D10 containing the three heavy chain CDRs, which are able to stimulate a specific immune response against HMFG. The specification discloses that a region consist of as few as five contiguous amino acids of the amino acid sequence of monoclonal antibody 11D10 (page 24). Accordingly, the genus to

which the claims are drawn includes polypeptides having widely variable structures. However, the specification only provides an adequate description of monoclonal antibody 11D10 and fails to teach how the one disclosed species is representative of the genus. As the presence of the three CDRs of the light chain, or the three CDRs of the heavy chain alone does not correlate with the ability of the members of the genus of polypeptides to stimulate a specific immune response against HMFG, one skilled in the art would not be expected to be capable of immediately recognizing at least a substantial number of the claimed polypeptides, as one skilled in the art could not predict which polypeptides comprising a region of monoclonal antibody 11D10 containing the three light chain CDRs, or alternatively a region of monoclonal antibody 11D10 containing the three heavy chain CDRs to stimulate a specific immune response against HMFG. Therefore, the disclosure would not reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed.

Claim 27 and its dependent claims are drawn to a fusion polypeptide comprising the polypeptide of claim 20. The specification discloses that while a fusion polypeptide can comprise a heterologous amino acid sequence, the term is also used to encompass a polypeptide comprising jumbled regions of the amino acid sequence of another protein from which the fusion polypeptide is derived (paragraph bridging pages 24 and 25). Accordingly, the genus to which the claims are drawn includes polypeptides having widely variable structures. However, if monoclonal antibody 11D10 is meant to be representative of the claimed genus of fusion polypeptides, it is unclear how it is so. While the skilled artisan could envision a single-chain Fv antibody derived from monoclonal antibody 11D10, which would be a fusion polypeptide comprising the amino acid sequence of the light chain of monoclonal antibody 11D10 and the amino acid sequence of the heavy chain of the monoclonal antibody and would be reasonably expected to be able to stimulate a specific immune response against HMFG, the genus of fusion polypeptides also encompasses a wide variety of structurally different polypeptides in which, for example, the spatial relationship of the CDRs has been altered. The presence of the three CDRs of the light chain and/or the three CDRs of the

heavy chain alone does not correlate with the ability of the members of the genus of polypeptides to stimulate a specific immune response against HMFG. Therefore, one skilled in the art would not be expected to be capable of immediately recognizing at least a substantial number of the claimed polypeptides. Therefore, the disclosure would not reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed.

Claims 1, 3, 20, 35, 39, 73, and 84, and the claims that depend from these claims, are drawn to an antibody or a polypeptide comprising a portion of the antibody, wherein the antibody is produced by the hybridoma deposited under ATCC Accession No. HB-12020 *or progeny thereof.* The specification defines the term "progeny" of a hybridoma as "descendents of a hybridoma, which may or may not be completely identical to the original (parent) cell due to mutation or other adaptation, but that produce a monoclonal antibody that maintains the ability to escape immune tolerance, i.e., to cause an immune response against HMFG" (page 20, lines 8-11). However, the specification only describes the monoclonal antibody 11D10, which is produced by the hybridoma deposited under ATCC Accession No. HB-12020. The specification does not adequately describe a representative number of, or at least a substantial number of members of the claimed genus of polypeptides comprising an immunoglobulin variable region of the antibodies produced by the progeny of the hybridoma deposited under ATCC Accession No. HB-12020, which according to the specification may differ from the antibody produced by the parental cell, namely 11D10. Although the claim requires the polypeptide to be capable of stimulating a specific immune response against HMFG, this does not adequately describe the members of the claimed genus of polypeptides and antibodies, but merely states what the polypeptides must be capable of doing.

Claim 26 recites "a sequence in human mucin", but the specification does not include an adequate description of "human mucin". Because one skilled in the art could not recognize human mucin, or differentiate human mucin from other mucins, one skilled in the art could not recognize the members of the claimed genus of polypeptides.

Claims 35, 64, 65, 72, 73, and 80-87 are drawn to a genus of humanized antibodies comprising the three CDRs of the light chain of monoclonal antibody 11D10

and the three CDRs of the heavy chain of the monoclonal antibody. Claims 88-95 are drawn to a genus of antibodies comprising mere regions of the light and heavy chains of monoclonal antibody 11D10, or comprising the three CDRs of the light chain of monoclonal antibody 11D10 and the three CDRs of the heavy chain of the monoclonal antibody but in no particular order. Because the spatial arrangement of the CDRs is not specified, the claims encompass a large genus of structurally variant antibodies. Claims 92-95 do not recite a limitation requiring the claims antibodies to have any particular function. The remainder of the claims recite a limitation requiring the members of the claimed genus of antibodies to have a particular function, but the presence of the three CDRs of the light chain and/or the three CDRs of the heavy chain alone does not correlate with the ability of the members of the genus of humanized antibodies to stimulate a specific immune response against HMFG. Therefore, one skilled in the art would not be expected to be capable of immediately recognizing at least a substantial number of the claimed polypeptides. Therefore, the disclosure would not reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of highly variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicants in the specification; nor have Applicants shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor have Applicants described distinguishing identifying characteristics sufficient to show that Applicants were in possession of the claimed invention at the time the application was filed.

Skolnick, et al (*Trends in Biotechnology* **18**: 34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). The unpredictable nature of the art is further underscored by the teachings of Rudikoff, et al, Panka, et al, and Amit, et al (cited *supra*). Thus, one skilled in the art would not accept the assertion that a polypeptide comprising the three light chain and/or the three heavy chain CDRs of monoclonal antibody 11D10 would be capable of stimulating a specific immune response against

HMFG. Therefore, as evidenced by the teachings of Skolnick, et al, the art is unpredictable.

The *Guidelines* state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 26 and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 is indefinite. The metes and bounds of the invention cannot be determined, since the claim lacks clarity. Applicants are required to amend the claim to more particularly point out and distinctly claim the subject matter that Applicants regard as the invention, or must provide an explanation of the claim.

Claim 56 recites "the 11D10 polypeptide of claim 20". There is insufficient antecedent basis in claim 20 for recitation of this limitation in claim 56.

Claim Rejections – 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

21. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

22. Claims 1-5, 37, 40, 59, 60, 69, 70, 74, 75, 88-90, 92-94, and 97 are rejected under 35 U.S.C. 102(b) as being anticipated by Bhattacharya-Chatterjee, et al (In *Antigen and Antibody Molecular Engineering in Breast Cancer Diagnosis and Treatment,* Ceriani, RL, Ed., Plenum Press: New York, pp. 139-148, 1994).

Bhattacharya-Chatterjee, et al teach methods for making, characterizing, and using monoclonal antibody 11D10. Bhattacharya-Chatterjee, et al teach detectably labeled monoclonal antibody 11D10.

Even though the prior art does not explicitly disclose the hybridoma having the ATCC accession no. HB 12020, as it appears that the monoclonal antibody of the prior art is the same as an antibody encompassed by the claims, the prior art provides evidence that the hybridoma or its progeny that are encompassed by the claims were in public use in this country more than one year before the earliest effective filing date sought by Applicants, because the claimed antibodies could not have been made without the claimed hybridoma or its progeny.

Applicants have traversed this ground of rejection arguing that since neither monoclonal antibody 11D10 nor the hybridoma that produces the monoclonal antibody were publicly available before the effective filing date sought by Applicants in this application, although the references disclose the antibody, the references are not enabling of the claimed invention.

To support their argument, Applicants have submitted a declaration under 37 CFR § 1.132 by Malaya Bhattacharya-Chatterjee that states: (a) the hybridoma and the

antibody had been maintained exclusively under the control of the declarer, (b) there has been no free exchange of the hybridoma or the antibody, and (c) neither the hybridoma nor the antibody were released to the public before the filing of this application or before the filing date of US provisional application Serial No. 60/031,306. Furthermore, the declaration by Malaya Bhattacharya-Chatterjee states that none of Ewe Mrozek, Sonjoy Mukerjee, Mala Chakraborty, Roberto Ceriani, Heinz Kohler, and M. Sherratt distributed the antibody or the hybridoma to anyone outside of the laboratory.

Additionally, Applicants have submitted a declaration under 37 CFR § 1.132 by Sunil K. Chatterjee that states: (a) the hybridoma producing monoclonal antibody 11D10 was used in the declarer's laboratory under his strict and exclusive control, (b) no one in his laboratory took the antibody or the hybridoma and no one had permission to do so, (c) the public did not have access to the hybridoma or the antibody at any time before the filing date the application, and (d) the declarer did not make the antibody or hybridoma available to the public.

Also, Applicants have submitted a declaration under 37 CRF § 1.132 by Kenneth A. Foon that states the public did not obtain the hybridoma or the antibody at any time before the filing date the application.

In response to Applicants' arguments, it is agreed that if neither the antibody nor the hybridoma producing the antibody were accessible or available upon request to any other individual that although the cited references disclose the antibody, none of the cited references can be considered to provide an enabling disclosure of the claimed invention. Consequently, it is necessary to determine whether or not someone other than any one of the co-inventors had access, or upon request could have acquired either the antibody or the hybridoma producing the antibody before the effective filing date sought by Applicants in this application.

In response to the declaration by Malaya Bhattacharya-Chatterjee, it is noted that the declaration does not explicitly state how the hybridoma and the antibody were controlled. Although the declaration states that neither the hybridoma nor the antibody was distributed to any other party before the effective filing date sought by Applicants in

this application, the declaration does not state that the hybridoma and the antibody were not publicly accessible, or available upon request.

Furthermore, with regard to the statements that none of Ewe Mrozek, Sonjoy Mukerjee, Mala Chakraborty, Roberto Ceriani, Heinz Kohler, and M. Sherratt distributed the antibody or the hybridoma to anyone outside of the laboratory, it is noted that this is hearsay evidence, which has not been supported by the declarations of any of Ewe Mrozek, Sonjoy Mukerjee, Mala Chakraborty, Roberto Ceriani, Heinz Kohler, or A.J. Sherrattt. Also, the declaration states that M. Sherratt did not distribute the antibody or the hybridoma to anyone outside of the laboratory, but A.J. Sherratt is the individual in question. Additonally, on page 5 of the declaration, it is stated, "[t]o the best of my knowledge and belief, the public **did** have access to the cell line" (emphasis added) (paragraph 1).

In response to the declaration by Sunil K. Chatterjee, although the declaration states that the hybridoma producing monoclonal antibody 11D10 was used in Dr. Chatterjee's laboratory under his strict and exclusive control, the declaration does not explicitly state how the hybridoma and the antibody were controlled. While the declaration states that no one in his laboratory took the antibody or the hybridoma, or had his permission to do so, and that the public did not have access to the hybridoma or the antibody at any time before the filing date of this application, the declaration does not state that the antibody or the hybridoma could not have been obtained upon request.

Also, on page 3 of the declaration, it is stated, "[t]o the best of my knowledge and belief, the public **did** have access to the cell line" (emphasis added) (paragraph 3).

In response to the declaration by Kenneth A. Foon, although the declaration states that monoclonal antibody 11D10 was used in clinical studies under strict and exclusive control and further states who had access to the antibody and to whom the antibody was given, the declaration does not explicitly state how the antibody was controlled. Although the declaration states the public did not obtain the hybridoma or the antibody at any time before the filing date of the application, the declaration does

not state that the antibody and the hybridoma were not publicly accessible, or attainable upon request.

Accordingly, it cannot be ascertained whether or not the monoclonal antibody 11D10 or the hybridoma producing the monoclonal antibody were publicly accessible or attainable upon request before the filing date of this application.

Nevertheless, the present claims are not limited to monoclonal antibody 11D10, or to the hybridoma deposited under ATCC accession no. HB 12020; rather the claims are drawn to a genus of polypeptides, including fusion proteins and antibodies, that are capable of stimulating a specific immune response against HMFG, some of which are produced by the progeny of the hybridoma that produces monoclonal antibody 11D10. Accordingly, the declarations fail to provide a showing that is reasonably commensurate in scope with the claims. Furthermore, contrary to Applicants' assertions, the prior art is enabling of the presently claimed invention, since the claims are not limited to monoclonal antibody 11D10 or derivatives thereof, *per se,* and one would not necessarily have to have access to the hybridoma producing monoclonal antibody 11D10 to make and use the claimed invention. Consequently, Applicants' arguments and the merit of the declarations by the co-inventors have been carefully considered but have not been found persuasive.

23. Claims 1, 3-5, 37, 40, 59, 60, 69, 70, 74, 75, 88-90, 92-94, and 97 are rejected under 35 U.S.C. 102(b) and/or 35 U.S.C. 102(a) as being anticipated by Bhattacharya, et al (*Cancer Immunology & Immunotherapy* **38**: 75-82, 1994) or Chakraborty, et al (*Proceedings of the American Association for Cancer Research* **35**: 497, Abstract No. 2963; 1994).

Bhattacharya, et al and Chakraborty, et al disclose that monoclonal antibody 11D10 was known and used by others in this country before the earliest effective filing date sought by Applicants. In addition, the abstract of Chakraborty, et al provides evidence that the use of the antibody was disclosed publicly during a poster session at a scientific meeting.

24. Claims 1, 3-5, 37, 40, 59, 60, 69, 70, 74-76, 88-95, and 97 are rejected under 35 U.S.C. 102(a) as being anticipated by Charkraborty, et al (*Cancer Research* **55**: 1525-1530, 1995).

Chakraborty, et al teach a composition comprising monoclonal antibody 11D10 and an adjuvant, which when administered to a monkey stimulates a specific immune response against HMFG.

Even though the prior art does not explicitly disclose the hybridoma having the ATCC accession no. HB 12020, as it appears that the monoclonal antibody of the prior art is the same as an antibody encompassed by the claims, the prior art provides evidence that the hybridoma or its progeny that are encompassed by the claims were in public use in this country more than one year before the earliest effective filing date sought by Applicants, because the claimed antibodies could not have been made without the claimed hybridoma or its progeny.

Applicants have traversed the ground of rejection of the claims under 35 USC § 103(a) as being anticipated by Charkraborty, et al (*Cancer Research* **55**: 1525-1530, 1995) by submitting a declaration under 37 CFR § 1.132 by Malaya Bhattacharya-Chatterjee, Ph.D. The merit of Applicants' submission has been carefully considered but is insufficient to overcome the grounds of rejection under 35 USC § 103(a).

The declaration by Dr. Bhattacharya-Chatterjee states that Sonjoy Mukerjee was a post-doctoral fellow working under Dr. Bhattacharya-Chatterjee's supervision and under Dr. Bhattacharya-Chatterjee's supervision, Dr. Mukerjee participated in generating and characterizing monoclonal antibody 11D10. The declaration further states that Roberto Ceriani and Heinz Kohler did not participate in any way in generating or characterizing monoclonal antibody 11D10.

The declaration is insufficient because the declaration appears to state that Dr. Mukerjee made an inventive contribution, athough Dr. Ceriani and Kohler did not. Post-doctoral fellows are highly trained and highly skilled. Post-doctoral fellows are generally capable of working independently; and it appears that Dr. Mukerjee was not the exception, since it appears he made an independent inventive contribution in generating

the hybridoma and the antibody, and in characterizing the identifying features of the antibody.

25. Claims 1, 3-5, 37, 40, 59, 60, 69, 70, 74, 75, 88-90, 92-94, and 97 are rejected under 35 U.S.C. 102(a) as being anticipated by Chakraborty, et al (*Journal of Immunotherapy* **18**: 95-103, 1995).

Chakraborty, et al disclose monoclonal antibody 11D10 and it use. Chakraborty, et al reference other publications describing the production of monoclonal antibody 11D10.

Applicants have traversed this ground of rejection by submitting the declarations under 37 CFR 1.132. Applicants' arguments and the merit of these declarations have been addressed in the paragraphs above.

26. Claims 88-90 are rejected under 35 U.S.C. 102(b) as being anticipated by Kofler, et al (*Journal of Clinical Investigation* **82**: 852-860, 1988).

Kofler, et al teach an antibody comprising a light chain variable region amino acid sequence contained in SEQ ID NO: 2 and a heavy chain variable region amino acid sequence contained in SEQ ID NO: 4.

Claim Rejections - 35 USC § 103

27. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

28. Claims 1-5, 31-33, 35, 37, 40, 43, 54, 55, 59, 60, 64, 65, and 69-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bhattacharya-Chatterjee, et al (In *Antigen and Antibody Molecular Engineering in Breast Cancer Diagnosis and Treatment,* Ceriani, RL, Ed., Plenum Press: New York, pp. 139-148, 1994) in view of

Chakraborty, et al (*Proceedings of the American Association for Cancer Research* **35**: 497, Abstract No. 2963, 1994) and in further view of Kennedy, et al (*Biotechniques* **3**: 404-410, 1985), WO 94/11508-A2 (26 May 1994), Goldenberg (*American Journal of Medicine* **94**: 297-312, 1993), and Carter, et al (*Proceedings of the National Academy of Sciences of the USA* **89**: 4285-4289, 1992).

Bhattacharya-Chatterjee, et al teach a murine anti-idiotypic monoclonal antibody 11D10, which can be produced by immunizing a mammal with a monoclonal antibody that specifically binds human milk fat globule (HMFG) protein, namely BrE-1, and isolating a hybridoma that expresses the polynucleotide sequences encoding the light and heavy chains of a monoclonal antibody that binds specifically to the paratope of the monoclonal antibody BrE-1 (pages 140 and 141). Bhattacharya-Chatterjee, et al teach that the monoclonal antibody 11D10 elicits an anti-HMFG immunological response in mammals, namely mice and rabbits immunized with the antibody (page 142). Bhattacharya-Chatterjee, et al teach that patients diagnosed with breast cancer have Id matching sera, which suggests that the antibody may be specially suitable as a potential candidate agent for active anti-Id immunotherapy (page 144).

However, Bhattacharya-Chatterjee, et al do not teach that the murine anti-idiotypic monoclonal antibody 11D10 can be used as an immunogen to immunize a mammal to induce antitumor immunity in the immunized mammal by activating both humoral and cellular immune anti-HMFG immunological response in the mammal.

Nonetheless, Chakraborty, et al teach that anti-HMFG, Id-specific humoral and cellular immunological responses can be elicited in monkeys by immunizing the monkeys with monoclonal antibody 11D10. Chakraborty, et al conclude, "[t]hese results indicate that alum precipitated anti-Id 11D10 can induce breast cancer specific antibodies in non-human primates and can serve as a network antigen for breast cancer patients" (abstract).

Therefore, in view of the teachings of Chakraborty, et al it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made that the murine monoclonal antibody 11D10 of Bhattacharya-Chatterjee, et al, when used to immunize mammals having primed anti-HMFG B- and/or T-cells, is capable of

stimulating a specific immune response against HMFG in the immunized mammal by activating the primed B- and T-cells of the mammal, because Chakraborty, et al concluded that the antibody can induce breast cancer specific antibodies in mammals and can serve as a breast network antigen in patients diagnosed with breast cancer. One of ordinary skill in the art would have been motivated at the time the invention was made to use the murine monoclonal antibody 11D10 of Bhattacharya-Chatterjee, et al to immunize mammals having primed anti-HMFG B- and T-cells, because upon immunizing the mammal with the monoclonal antibody, the monoclonal antibody is capable of inducing antitumor immunity in the immunized mammal by activating the primed B- and T-cells of the mammal and thereby eliciting an anti-HMFG immunological response against breast cancer in the mammal.

However, Bhattacharya-Chatterjee, et al and Chakraborty, et al do not disclose a kit. Additionally, Bhattacharya-Chatterjee, et al and Chakraborty, et al do not teach a chimeric or humanized versions of monoclonal antibody 11D10, which comprise the three CDRs of light and heavy chains of monoclonal antibody 11D10, or a fusion polypeptide or a single-chain antibody comprising the variable regions of the light and heavy chains of monoclonal antibody 11D10 joined by a linker of about 5 to about 20 amino acids, or a linker comprising SEQ ID NO: 35.

Nevertheless, Kennedy, et al teach that anti-idiotypic (anti-Id) immunization may offer a number of advantages and because anti-Id could be produced that mimic tumor antigens, an anti-Id vaccine might be capable of eliciting antitumor immunity in patients (page 408, column 1). Kennedy, et al teach that such anti-Id vaccines may be advantageous, because the anti-Id vaccine would induce immunity against a single epitope present on the tumors and bypass the risk of producing a deleterious autoimmune response against the host, which might occur if a vaccine is composed of a protein, attenuated virus, or killed cell, which shares antigenic determinants with the host. However, Kennedy, et al also teach that anti-Id immunization has a potential disadvantage, namely the need to repeatedly immunize the host to boost the immunological response, which can be dangerous since repeated immunizations may trigger anaphylaxis, i.e., a severe and sometimes fatal adverse immune reaction, in the

immunized animal (page 408, column 2). On the other hand, Kennedy, et al teach, "methods are becoming available to produce chimeric antibody molecules in which the V region is of mouse origin and the rest of the molecule is human in nature" (page 408, column 2). Kennedy, et al teach that the production of such chimeric antibodies would be advantageous because such chimeric antibodies could be administered to patients, thereby lessening the potential for producing anaphylaxis as a result of multiple injections of an anti-Id vaccine preparation (page 408, column 2).

Additionally, WO 94/11508-A2 teaches methods for producing anti-idiotypic chimeric antibodies that bind specifically to the paratope of anti-HMFG antibodies (pages 33 and 34, Example 12; pages 42 and 43, Example 29). Furthermore, WO 94/11508-A2 teaches that such anti-idiotypic antibodies are suitable for immunizing humans against neoplasias, i.e., cancer (page 1) and teaches methods for treating humans with immunogenic compositions comprising the chimeric antibodies (claim 54, for example).

Goldenberg reviews antibodies and derivatives thereof, including anti-idiotypic antibodies. Goldenberg teaches that the effectiveness of antibody-mediated therapy is hampered by human anti-mouse immune response. Although an anti-anti-idiotypic immune response is desirable, the stimulation of an immune response against the constant regions of the mouse monoclonal antibody, for example, is not desirable. Goldenberg discuss the advantages provided by using humanized or chimeric versions of monoclonal antibodies.

Carter, et al teach methods for producing humanized versions of monoclonal antibodies.

Therefore, in further view of the teachings of Bhattacharya, et al and WO 94/11508-A2, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to construct a single chain chimeric antibody that has the same binding specificity as monoclonal antibody 11D10. In view of the teachings of Goldenberg and Carter, et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced a humanized version of monoclonal antibody 11D10 or of an antibody that comprises the three CDRs

of both the light and heavy chain immunoglobulin variable domains of monoclonal antibody 11D10 that stimulates a specific immune response against HMFG. One of ordinary skill in the art at the time the invention was made would have been motivated to have done so, because of the advantages provided by chimeric and humanized antibodies.

In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to manufacture a kit comprising the monoclonal antibody 11D10 with or without a detectable label, because kits provide greater ease to practicing a method and are convenient.

29. Claims 1-5, 31-33, 35, 37, 40, 43, 54, 55, 59, 60, 64, 65, and 69-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakraborty, et al (*Cancer Research* **55**: 1525-1530, 1995) in view of Kennedy, et al (*Biotechniques* **3**: 404-410, 1985) and WO 94/11508-A2 (26 May 1994) and in further view of Goldenberg (*American Journal of Medicine* **94**: 297-312, 1993) and Carter, et al (*Proceedings of the National Academy of Sciences of the USA* **89**: 4285-4289, 1992).

Chakraborty, et al teach immunization of monkeys with murine monoclonal antibody 11D10 induces antitumor immunity in the animals (abstract). Chakraborty, et al disclose, "[a]ll monkeys developed high titers of antibodies against the immunizing mouse immunoglobulin [...] which reacted with breast cancer cell lines" (abstract). The antibodies produced in the monkeys reacted bound specifically to human milk fat globule (HMFG) protein (abstract). Chakraborty, et al also teach that immunization of mice and rabbits with the monoclonal antibody also induced antitumor immunity in those animals, suggesting that the antibody is capable of inducing immune responses across species barriers (abstract), thus Chakraborty, et al teach that the antibody elicits an anti-HMFG immunological response in mammals. Furthermore, Chakraborty, et al teach that the immunized monkeys developed cellular immune responses as demonstrated by T-cell proliferation assays (abstract). Chakraborty, et al teach that the same adjuvant and dose of the monoclonal antibody, which will be used in clinical trials, was used to immunize the monkeys (page 1525, column 2). Chakraborty, et al teach that the final

immunogenic composition, which was used to immunize the monkeys, was prepared aseptically and was therefore sterile (page 1526, column 1). Chakraborty, et al conclude, "[t]hese studies, therefore, are likely to predict the safety and efficacy of this anti-Id to induce antitumor antibodies in breast cancer patients" (page 1525, column 2).

However, Chakraborty, et al do not teach a fusion polypeptide or a single-chain antibody that comprises the light chain and heavy chain variable domains of monoclonal antibody 11D10; nor do they disclose a chimeric or humanized version of monoclonal antibody 11D10. Also, Chakraborty, et al do not disclose a kit.

Kennedy, et al, WO 94/11508-A2, Goldenberg, and Carter, et al teach that which is set forth in the 35 USC § 103(a) rejection above.

Therefore, in view of the teachings of Kennedy, et al and WO 94/11508-A2, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a polypeptide comprising the light and heavy chain variable regions of the mouse monoclonal antibody 11D10 of Chakraborty, et al, or a single chain chimeric antibody that has the same binding specificity as monoclonal antibody 11D10. In further view of the teachings of Goldenberg and Carter, et al, it would have been *prima facie* obvious to have produced a humanized version of monoclonal antibody 11D10 or of an antibody that comprises the three CDRs of both the light and heavy chain immunoglobulin variable domains of monoclonal antibody 11D10 that stimulates a specific immune response against HMFG. One of ordinary skill in the art at the time the invention was made would have been motivated to have done so, because of the advantages provided by chimeric and humanized antibodies.

One of ordinary skill in the art at the time the invention was made would have been motivated to manufacture a kit comprising monoclonal antibody 11D10 or a derivative thereof, and more particularly, comprising detectably labeled monoclonal antibody 11D10, because kits provide greater ease to practicing a method and are convenient.

Applicants have traversed this ground of rejection arguing that the cited references failed to provide enabling disclosure of the claimed invention, while noting "the Examiner alleges that there is evidence to the contrary in the form of the publication

policy of Cancer Research, requiring authors to make freely available biological materials that were used in the research reported" (page 12, paragraph 1). Although it is noted that Applicants' representative stated her awareness of the publication policy of the journal *Cancer Research* in Paper No. 19 (page 8), Applicants remarked later in Paper No. 26, "the publication policy of Cancer Research did not serve to place the 11D10 hybridoma into the hands of the public by virtue of Applicants publishing their research in this journal" (page 13, paragraph 3). "Applicants respectfully submit that the journal merely has a policy that authors agree to make freely available to others materials used in reported research, but does not require that the authors do so."

In response to Applicants' argument, the reference cited as a basis of rejection under 35 USC § 102(a) was published in the April 1 issue of 1995. The journal of *Cancer Research* publishes Instructions for Authors in the first issue of the year, so therefore the Instructions for Authors, which appeared in the January 1 issue of 1995, were applicable at the time the authors of the prior art reference published a report of their research. The Instructions for Authors includes the journal's Policy Concerning Availability of Materials (page 207, column 1), which states:

> It is understood that by publishing any work in *Cancer Research* the authors agree to make freely available to other academic researchers any cells, clones of cells or DNA or antibodies, etc. that were used in the research reported and that are not available from commercial suppliers.

In view of the journal's Policy Concerning Availability of Materials it appears that by publishing any work in the journal, which the authors of the cited prior art reference did, the authors acknowledged and accepted the policy, agreeing to make freely available to other academic researchers any cells, clones of cells, or antibodies that were used in the research reported. Because the cited prior art reference published in Cancer Research discloses the use of monoclonal antibody 11D10 and the hybridoma that produces the monoclonal antibody, it appears that the monoclonal antibody and the hybridoma were attainable, upon request, by any academic researcher, provided that the authors were willing and able to comply with the acknowledged and accepted policy of the journal. Consequently, contrary to Applicants' assertions, monoclonal antibody

11D10 and the hybridoma that produces the antibody should have been attainable upon request by another party.

For the reasons stated above, the declarations filed under 37 CFR §1.132 by the co-inventors stating that neither monoclonal antibody nor the hybridoma that produces the monoclonal antibody were distributed to any person other than those individuals whom were working under the direct supervision of the co-inventors are deficient. The fact that Applicants' did not distribute the antibody or the hybridoma to any other person does not constitute evidence that the antibody and the hybridoma were not accessible or attainable upon request by another. In fact, the Policy Concerning Availability of Materials of the journal of *Cancer Research* would suggest that to the contrary of Applicants' assertion, the antibody and the hybridoma were at least attainable by another upon request. Applicants' arguments have been carefully considered but not found persuasive.

Double Patenting

30. The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time-wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

31. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

32. Claims 1-5, 37, 40, 43, 54, 55, 59, 60, 69, 70, 74-76, and 88-97 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 37, 40, 43, 54, and 55 of co-pending Application No. 08/836,455. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of claims 1-5, 37, 40, 43, 54, 55, 59, 60, 69, 70, 74-76, and 88-97 of the instant application is anticipated by claims 1-5, 37, 40, 43, 54, and 55 of the co-pending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

33. No claims are allowed.

34. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The disclosure of Zeytin, et al, Gavilondo, et al, Bodey, et al, Yu, et al, and Bocchia, et al are pertinent to the claimed invention, as each demonstrates the state of the art. Basham, et al, Berinstein, et al (1987 and 1988), and Hurwitz, et al teach that anti-idiotypic antibodies and chemotherapeutic agents, including IL-2, exhibit synergistic or additive behavior. Campbell, et al teach that both arms of the immune system need to be stimulated, if idiotype vaccination is to be successful. Tao, et al and Chen, et al teach a fusion protein comprising an idiotype and GMSCF or IL-2. Alfthan, et al teach single-chain antibody construction.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is

(703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr

February 3, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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